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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,377	10/30/2000	Toshikazu Nakamura	Q 61434	7003

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,377	NAKAMURA, TOSHIKAZU	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,12-15,19,20 and 28-37* is/are pending in the application.

4a) Of the above claim(s) *16 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,12-15,19,20 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-4,6,12-15,19,20 and 28-37* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 6, 12-16, 19, 20, and 28-37 are pending.

Claims 1-4, 6, 12-15, 19, 20, and 28-36 are under consideration.

The rejection of claims 7, 9, 10, 14, 15, 21, 22, 25, 26, 28-30 and 33-36 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions for and methods of antagonizing HGF to inhibit or treat neovascularization, including inhibition of tumor growth or metastasis, does not reasonably provide enablement for prophylaxis is withdrawn in view of applicants amendments.

The rejection of claims 1-5, 7, 9 and 10 under 35 U.S.C. 102(b) as being clearly anticipated by Date et al., FEBS Lett. 420:1-6, is withdrawn in view of applicants amendments.

Terminal Disclaimer

The terminal disclaimer filed on 9/18/2006 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No.6,855,685 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Accordingly, all double patenting rejections have been overcome.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 4/28/1998. It is noted, however, that applicant has not filed a certified copy of the JPO application as required by 35 U.S.C. 119(b).

Applicants request that the Examiner acknowledge receipt of the priority document is noted. However, the Examiner cannot acknowledge that which is not present in the file. Given that the prior art applied pre-dates the claimed foreign priority, the point appears moot.

Drawings

The new drawings are acknowledged.

Specification

The substitute specification is acknowledged.

The new title of the invention is acknowledged.

Claim Objections

37 C.F.R.§1.821(d) reads as follows:

> (d) Where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The claims and/or specification are not in full compliance with 37 C.F.R.§1.821(d), and should be amended to refer to the appropriate sequence identifier(s) (SEQ ID NO:). For example, see claims 1-2, 12-15, 28, 31, and 34, and page 30 of the specification. Correction is **required.**

Applicants have traversed that the above requirement is not needed. This argument has been fully considered but is not deemed persuasive because there is ambiguity in the numbering of hHGF, as set forth in the rejection under 35 U.S.C. §112, second paragraph in the previous Office Action mailed 3/16/2006. As the sequence of hHGF is *essential subject matter*, the Examiner finds that it must be appropriately disclosed in the specification, and appropriately referred to in the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 19 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim reads on a product of nature.

Applicants have traversed this rejection, stating that the protein is not a naturally occurring one. This argument has been fully considered but is not deemed persuasive because the 5 amino acid deletion was obtained from a natural source by Nakamura, and elastase is an enzyme that naturally occurs in humans. Hence, there is no assurance that the molecule does not occur naturally. Applicants are reminded that although *they* may not have obtained the protein from nature, the claims are not product by process claims, nor would such a limitation be deemed appropriate in view of the aforementioned.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 12-15, 19, 20, and 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims which refer to amino acid residues by number without reference to a SEQ ID NO:, such as claims 1-2, 12-15, 28, 31, and 34, are indefinite. Numbering is not inherent to a protein. For example, the residue referred to by applicants as "$PyrGlu^{32}$" is actually the first residue of the mature HGF protein, and thus referred to in the art as residue 1. Further, when the residue *is* at position 32, it is not PyrGlu, but rather glutamine, as the modification to become PyrGlu occurs *after* cleavage of the 31 amino acid leader sequence. Also, the recitation "$PyrGlu^{32}$~Val^{478}" is further indefinite because it is internally inconsistent: If one is numbering so that the PyrGlu is at residue 32, then the valine in question would be at residue 509, not residue 478. It is only if one numbers the PyrGlu as residue 1 (of the mature protein) that there occurs a valine at position 478, and only (insofar as the Examiner can determine) with reference

to human and mouse HGF. Finally, the recitation "PyrGlu^{32}~Val^{478}" is further indefinite because the use of the tilde "~" to show a range of amino acids is not standard in the art, and might mean either a definite fragment consisting of residues 32-478, or alternatively a fragment that comprises from residue 32 to "approximately" residue 478, as the mathematical use of the tilde is to denote an approximation. Accordingly, the metes and bounds of the claims cannot be determined.

Applicants have argued that the numbering is "conventional". This argument has been fully considered but is not deemed persuasive because of the internal inconsistencies, as set forth in the paragraph above.

Claims 1, 2, 12-15, 28, 31 and 34 are further indefinite because they include "deletion, substitution or addition of one *or several* amino acids". While amended from "or more", which was found to have no upper limit on the number of such modifications, such that the claims are essentially single means claims, and one cannot determine whether a given molecule is or is not within the scope of the claims, the claims remain indefinite. The term "or several" in the claims is a relative term which renders the claim indefinite. The term "several" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. While the claims are not required to express the claimed invention with mathematical precision, the term does not clearly inform one how much variation is allowed.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 12-15, 28, 31 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 12-15, 28, 31 and 34 lack adequate written description because they include "deletion, substitution or addition of one or several amino acids" with no upper limit on the number of such modifications, such that the claims are essentially single means claims. The specification discloses a single HGF molecule, SEQ ID NO: 1, and a single mutein of SEQ ID NO: 1 lacking five amino acids, SEQ ID NO: 2. HGF is well known in the art. However, the claims do not require any conserved structure, but merely require that the "derived" sequence share function with the disclosed proteins. The specification provides no specific guidance as to what changes can be made in HGF within the scope of the claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 1 and 2, and HGF comprising residues 1-478 of art-recognized HGF, but not the full breadth of the claim meets the written description provision of

35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants argue, both with respect to this rejection and to the rejection under 35 U.S.C. §112, second paragraph, that the Examiner's reading of the claims is unreasonable. This argument has been fully considered but is not deemed persuasive because the Examiner is to read the claims as broadly as reasonable. In the absence of any teaching that would reasonably limit the claims, the Examiner must interpret them as being very broad. It remains that the "invention" herein is a truncated hHGF with a single 5 amino acid deletion, which disclosure does not evince conception of the scope of variants claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al. in view of Nakamura et al., EP 0461560, cited by applicants.

Date discloses HGF variant HGF/NK4, which is the same molecule as SEQ ID NO: 1 of the instant application. The protein was used to examine the mitogenic activity on rat hepatocytes in primary culture (page 4 and Figure 3), and thus would necessarily have been in a pharmaceutically acceptable formulation. The protein was made in CHO cells. At page 31 of

the specification as filed, it is disclosed that the protein, a made by CHO cells, has an N-terminus of Pyr-Glu.

The claims, which are specific to SEQ ID NO: 2, differ from the disclosure of Date et al. in that SEQ ID NO:2 has a deletion of 5 amino acids relative to the protein of SEQ ID NO: 1.

Nakamura et al., disclose a variant of HGF comprising the same 5 amino acid deletion relative to SEQ ID NO: 1 as found in SEQ ID NO: 2, see Figure 3 and claim 3. They disclose the protein having that 5 amino acid deletion to have HGF activity, and thus to be able to bind to HGF receptors.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the protein of Nakamura et al. in the teachings of Date et al. to produce an HGF inhibitor having the 5 amino acid deletion taught by Nakamura et al., to be used in pharmaceutical compositions as an HGF antagonist, as taught by Date et al. The person of ordinary skill in the art would have been motivated to do so by Nakamura's implicit teachings that the deleted protein was considered to be functionally equivalent to the other form of HGF, and would have expected success for the same reason. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

The declaration by Dr. Matsumoto under 37 CFR 1.132 filed 9/18/2006 is insufficient to overcome the rejection of claims based upon Date et al. in view of Nakamura et al as set forth in the last Office action because:

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

The nature of the fact to be established is an unexpected result, namely applicants assert that the finding that the claimed protein inhibits HGF induced growth of vascular endothelial cells and inhibits growth induced by bFGF and VEGF is unexpected. Declarant states that the results in figure 1 of the declaration demonstrate the unexpected result. However, the data in the declaration notably exclude a control in which the claimed protein is compared to Date's protein.

Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP §716.02(d) - § 716.02(e). See In re Blondel, 499 F.2d 1311, 1317, 182 USPQ 294,298 (CCPA 1974) and In re Fouche, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433(CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a prima facie case of obviousness. (MPEP 716.02(b)(III)). In this case, applicants seek to relate the data in the declaration to the claimed protein as compared to Date's protein by reference to a paper by Kuba et al., see page 21 of the response filed 9/18/2006. The quotation from Kuba at the top of page 22 of the response indicates that both NK4, which differs from the claimed protein only by the 5 amino acid deletion, and K1-K4, which omits the N-terminus of the protein, "retained inhibitory effects on endothelial proliferation and migration mediated by bFGF, VEGF, and HGF." This constitutes *opposing* evidence to applicants/declarants assertions. Simply put, both molecules tested by Kuba indicate that one would expect the very result that applicants allege is unexpected, as the properties are possessed by the most closely related prior art molecules. Applicants and declarant have not proffered any evidence to lead one to believe that deletion of the 5 amino acids would alter these properties. In fact, one would expect the claimed molecule to behave similarly to NK4, in view of Nakamuras showing that the deletion did not affect binding activity, which the person of ordinary skill in the art would recognize would be an essential feature of an antagonist.

Claims 12-15 and 28-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwall et al., U.S. Patent No. 6,207,152 (priority date 2/17/1998) in view of Date et al. and Nakamura et al.

Schwall et al. teach the treatment of various cancers with HGF antagonist antibodies (see claims). In the detailed description at paragraph 23, they teach:

> The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer (small cell and non-small cell), gastrointestinal cancer, liver cancer, kidney cancer, pancreatic cancer, cervical cancer, bladder cancer. hepatoma, breast cancer, colon carcinoma, and head and neck cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by increased levels of HGF or overexpression or activation of HGF receptor in the mammal.

Schwall et al. do not teach a method in which a derivative of HGF is used as the antagonist.

The teachings of Date et al. and Nakamura et al. are summarized above. In addition to the above teachings, Date teaches in the introduction that HGF is known in the art to be a pleiotrophic growth factor that targets epithelial and endothelial cells, to be involved in branching tubular morphogenesis, tumor invasion, and to stimulate neovascularization in tumors. Date teaches at page 6 that the protein "may have therapeutic potential to prevent invasion and metastasis of various carcinoma cells." Accordingly, It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the protein found obvious above over Date et al. in view of Nakamura et al. to treat cancer or any other medical condition in which neovascularization is a problem, in view of Schwall's teachings, and would have expected success in view of Date's teachings that the protein (without the 5 aa deletion) is an effective HGF antagonist and Nakamura et al., teaching that the 5 amino acid deletion does not

affect binding activity, taken with Schwall's teachings of treating a wide variety of cancers with HGF inhibitors. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner